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09/068,293	05/06/1998	ZIV SANDALON	AEM96-01A	2169

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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
SANDALS, WILLIAM O	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/068,293	Sandalon et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 27, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-13, 16-20, 22-37, 41-43, and 45-47* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-13, 16-20, 22-37, 41-43, and 45-47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Amendments to the claims in Paper No. 19, filed February 27, 2002 have overcome the rejection of the claims under 35 USC 112, second paragraph in the previous office action, and the rejection is withdrawn.

2. Arguments and amendments to the claims in Paper No. 19 have overcome the rejections of the claims under 35 USC 112, first paragraph in the previous office action, and the rejections are withdrawn.

3. Arguments and amendments to the claims in Paper No. 19 have overcome the rejection of the claims under 35 USC 102 over Christensen et al., in the previous office action, and the rejection is withdrawn.

4. Arguments and amendments to the claims in Paper No. 19 have overcome the rejection of claims 6, 7, 9, 10, 12, 16-20, 22-25, 27-34, 41 and 42 under 35 USC 102 over Colomar et al., in the previous office action, and the rejection is withdrawn.

5. Arguments filed in Paper No: 19 regarding the rejection of claims 1, 2, 4 and 5 under 35 USC 102 over Colomar et al. have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

6. Arguments filed in Paper No: 19 regarding the rejection of the claims under 35 USC 103(a) have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

Drawings

8. New formal drawings are required in this application because recent changes to the MPEP, section 608.02(c) no longer allow deferral of submission of drawings pursuant to notification. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings.

Claim Objections

9. Claims 1, 6, 7, 20 and 27 are objected to because of the following informalities: Claims 1, 6, and 7 are headed by "(Thrice amended)". The header should state (Four times amended). Claim 20 is headed by "(Twice amended)". The header should state (Thrice amended). Claim 27 recites at lines 2-3 "nucleic acid has operably linked thereto DNA sequence". The word "a" should be inserted between "thereto" and "DNA". Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 2, 4-13, 16-20, 22-28 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 1 appears to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B **and** (emphasis added) C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat. 1925).

13. Claim 1 recites the limitation "said mammalian cell" in lines 14 and 20. There is insufficient antecedent basis for this limitation in the claim.

14. Claim 6 recites the limitation "said non-viral constituent" in line 1. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 7 recites the limitation "the construct" in line 3. There is insufficient antecedent basis for this limitation in the claim.

16. Claim 12 recites the limitation "said non-viral constituent" in line 1. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 12 recites the limitation "the construct" in lines 6 and 8. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble, otherwise the claims do not result in what is stated in the preamble. The preamble includes SV40 viruses which do not appear in the final step.

19. Claim 18 recites the limitation "said purified exogenous nucleic acid" in line 3. There is insufficient antecedent basis for this limitation in the claim.

20. Claim 25 recites the limitation "said purified exogenous nucleic acid" in lines 1, 3 and 10. There is insufficient antecedent basis for this limitation in the claim.

21. Claim 43 recites the limitation "the construct" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Colomar et al. (of record, "AS").

Colomar et al. taught (see especially the abstract, the introduction, materials and methods, the figures and the discussion) a complex comprising a semi-purified SV40 capsid protein and at least one other SV40 protein, which may be VP1, VP2, VP3 or agnoprotein, where the presence of these proteins are inherent in Colomar et al. The complex may comprise three capsid proteins and foreign DNA.

Response to Arguments

24. Amendments to claims 6, 12 and 18 have necessitated the new grounds for rejection above. Arguments set forth in Paper No. 19 regarding the limitation of "non-viral" exogenous nucleic acids do not apply to claims 1, 2, 4, and 5. Therefore these arguments over Colomar et al. are not relevant to the newly formed rejection above, and the arguments are not addressed with respect to this rejection.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. Claims 1, 2, 4-13, 16-20, 22-37, 41-43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colomar et al. (above) in view of Christensen et al. (of record), Carswell et al. (of record), Oppenheim et al. (J. Virol. Vol. 66, 1992, of record) and US Pat No. 5,863,541 (of record).

The claims are drawn to a complex comprising a semi-purified SV40 capsid protein and at least one other SV40 protein, which may be VP1, VP2, VP3 or agnoprotein, and a method of making the complex, . The complex may comprise three capsid proteins and exogenous DNA or RNA. The exogenous nucleic acid may contain an *ori*, and where the packaged nucleic acid is treated with nuclease to remove unpackaged nucleic acid. The DNA may be circular or linear. Also claimed is that the exogenous nucleic acid may be non-viral, or RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone.

Colomar et al. taught the invention described above and where the exogenous DNA may contain an *ori*, and Colomar et al. taught a method of *in vitro* construction of the complex where the packaged nucleic acid is treated with nuclease to remove unpackaged nucleic acid. The DNA may be circular or linear. The exogenous nucleic acid may encode a protein. Colomar et al. states at the abstract "addition of purified DNA of polyomavirus to the dissociated SV40 before lowering of the salt concentration showed that virus-like structures could be formed from SV40 proteins and a foreign DNA".

Colomar et al. did not teach the exogenous nucleic acid may be non-viral, RNA, or antisense, and/or may encode a receptor, structural protein, regulatory protein or hormone.

Christensen et al. (see the entire article) demonstrates the *in vitro* formation of SV40 semi-purified capsid proteins into virus-like particles then introducing DNA to form SV40 pseudovirions.

US Pat No. 5,863,541 taught (see especially the abstract, the summary, column 5 and the claims) the production of AAV capsid proteins which were allowed to self assemble into capsids with exogenous nucleic acid to give pseudoviruses. The exogenous nucleic acid may be DNA, RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone. The host cell may be a human cell.

Carswell et al. taught (see especially the abstract) the advantage of combining an SV40 agnoprotein with SV40 capsid proteins to facilitate the assembly of capsids.

Oppenheim et al. (see especially the abstract) taught the advantage of combining an SV40 ori sequence with SV40 capsid proteins to facilitate the assembly of capsids.

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Colomar et al. with the method of Christensen, US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because Christensen et al. taught the formation of SV40 pseudovirions *in vitro* for the purpose of delivery of *in vitro* packaged DNA into cells. The capsid proteins of US Pat No. 5,863,541 were assembled in a like manner to the instant claimed invention demonstrating inclusion of nucleic acids which encode various entities for delivery to cells. This is an obvious extension of the gene therapy teachings of Christensen et al. or Colomar et al. and because the AAV capsids of US Pat

No. 5,863,541 were used for the same purpose and demonstrated the generally accepted practice of making pseudovirions for delivery of exogenous nucleic acids and proteins to cells. The making of AAV pseudovirions and SV40 pseudovirions is equivalent for the purpose of delivering exogenous nucleic acids and proteins to cells. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40 capsids.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Colomar et al. with the method of Christensen et al., US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because US Pat No. 5,863,541 recited at column 3, lines 11-13, "[m]olecules which may be associated with or encapsidated into capsids include DNA, RNA, proteins, peptides, small organic molecules, or combinations of the same", continuing at lines 26-27, "[t]his system may be particularly advantageous in AAV gene delivery systems...". Then at column 4, lines 21-23, "[m]ethods for the *in vitro* construction of AAV capsids and for the *in vitro* packaging of these capsids are also provided." Colomar et al. recite at page 2785, column 2 "[t]hese experiments show that it is possible to reconstitute *in vitro* infectious virus-like particles". Therefore, the capsids of US Pat No. 5,863,541 and Christensen et al. or Colomar et al. were intended for the same purpose, where US Pat No. 5,863,541 utilized AAV capsids and Christensen et al. or Colomar et al. utilized SV40 capsids. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40

capsids. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Colomar et al. with Christensen et al., Carswell et al., Oppenheim et al. and US Pat No. 5,863,541.

Response to Arguments

27. Arguments set forth in Paper No. 8 assert that the AAV capsids of US Pat No. 5,863,541 are different from the instant SV40 capsids, and the comparison is invalid. US Pat No. 5,863,541 is relied upon here to show a well known use of capsid proteins to encapsidate foreign nucleic acids including antisense.

28. In response to applicant's arguments in Paper No. 8 against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

29. In response to applicant's argument in Paper No. 8 that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the references are justifiably combined since each of US Pat No. 5,863,541,

Carswell et al. and Oppenheim et al. was used to demonstrate well known and obvious elements which are used to study related subject matter as the instant SV40 virion encapsidation.

30. Arguments set forth in Paper No. 11 assert that there is no motivation to combine US Pat No. 5,863,541 with the primary references since US Pat No. 5,863,541 dealt exclusively with the use of AAV capsids, and does not teach the use of SV40 capsids for this purpose. US Pat No. 5,863,541 is used in the rejection to demonstrate that the inclusion of nucleic acids such as antisense nucleic acids and ribozymes into the capsids of viral particle for the purpose of introduction into a cell was well known to those of skill in the art. In support of this position, US Pat No. 6,107,062, filed on July 30, 1992 taught (see the summary at columns 4-5) the general use of capsids for the transport of antisense nucleic acids and ribozymes into cells which further supports the motivation to combine, and demonstrates the well known use of any viral capsid to introduce nucleic acids into a cell.

31. Arguments set forth in Paper No. 17 assert that the results of Colomar et al. with Polyoma virus DNA show that the teachings of Colomar et al. were unsuccessful in producing infective viral particles. Colomar et al. showed infective viral particles using SV40 DNA. Therefore, Colomar et al. did teach that reconstituted viral particles may be infective. Other limitations which are argued in Paper No. 17 are not present in the claims, and as such are not pertinent to the facts of the rejection.

32. Arguments set forth in Paper No. 19 assert that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

33. Arguments set forth in Paper No. 19 assert that Colomar et al. does not suggest the use of non-viral constituents in the method of *in vitro* packaging. Colomar et al. suggests the use of "foreign DNA" at the abstract.

34. Arguments set forth in Paper No. 19 assert that AAV particles of US 5,863,541 assembles "genetic material" into pre-formed capsids, which is different from the method of claim 18 and 29. US 5,863,541 recites at the abstract, introduction and summary that the *in vitro* packaging of foreign DNA into viral capsids for the delivery of the foreign DNA to target cells is desirable and useful. The foreign DNA of US 5,863,541 is packaged *in vitro* in one step, or alternatively in two steps as recited at sections 5.3 to 5.6. The teachings of US 5,863,541 are clear and reasonably suggest to one of ordinary skill in the art of the desirability and usefulness of packaging foreign DNA into capsids which have been formed from purified capsid proteins *in vitro*. Therefore, the arguments are not found persuasive.

35. Arguments set forth in Paper No. 19 assert that since the foreign polyoma DNA packaged into SV40 capsids *in vitro* in Colomar et al. was not infective, that the combination of Colomar et al. with the other references would have failed to make applicant's invention. Colomar et al.

recite at page 2784, column 1, bottom, that the infectivity of SV40 *in vitro* packaged polyoma DNA was about the same as naked polyoma DNA, and that the reason for this was unclear, since the SV40 capsid binds to and enters mouse cells. This demonstrates that Colomar et al. contemplated the delivery of foreign DNA to cells packaged into SV40 capsids *in vitro*. Colomar et al. make clear the fact that the foreign DNA was DNAase resistant when packaged *in vitro*, and therefore, properly packaged. Colomar et al. state at the abstract that the *in vitro* packaging of foreign DNA in SV40 capsids was a useful and desirable method for delivery of foreign DNA into cells. The fact that the foreign polyoma DNA was not infective, did not detract from the fact that the foreign DNA was delivered to the cells, and the question of why the DNA was not infective is left open for further investigation. The successful method of US 5,863,541 for production and infectivity of foreign DNA packaged *in vitro* by viral capsids made from purified viral capsid proteins is clearly suggested by this teaching of Colomar et al.

36. Arguments set forth in Paper No. 19 assert that Carswell et al. and Oppenheim et al. do not teach all of the elements of the instant invention. Carswell et al. and Oppenheim et al. recite well known teachings on the agnoprotein and *ori* respectively which show that these elements were well known in the art, and were desirable and useful in the assembly of SV40 virus capsids which infect mammalian cells.

37. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is found in the abstract of Colomar et al. and in the introduction and summary of US 5,863,541 where they both teach the useful and desirable *in vitro* packaging of foreign DNA into viral capsids which had been formed from purified or semipurified capsid proteins.

38. In response to applicant's arguments in Paper No. 19 against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

39. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

40. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of

such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
May 15, 2002

TERRY MCKELVEY
PRIMARY EXAMINER